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# ARCHIVES OF PEDIATRICS

Albro C. Gaylor, Publisher

JOHN FITCH LANDON, *M.D., Editor*

Vol. 77 No. 1

January 1960



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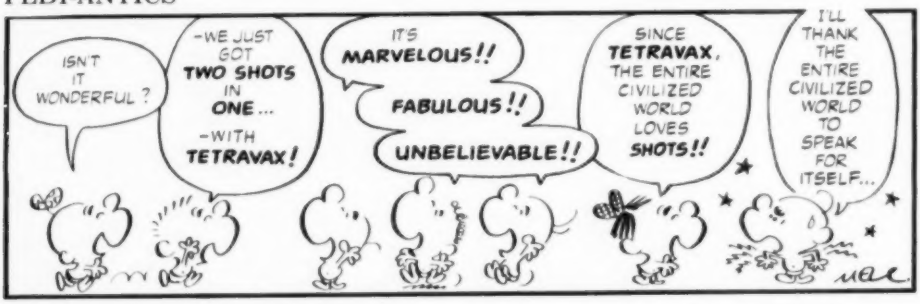


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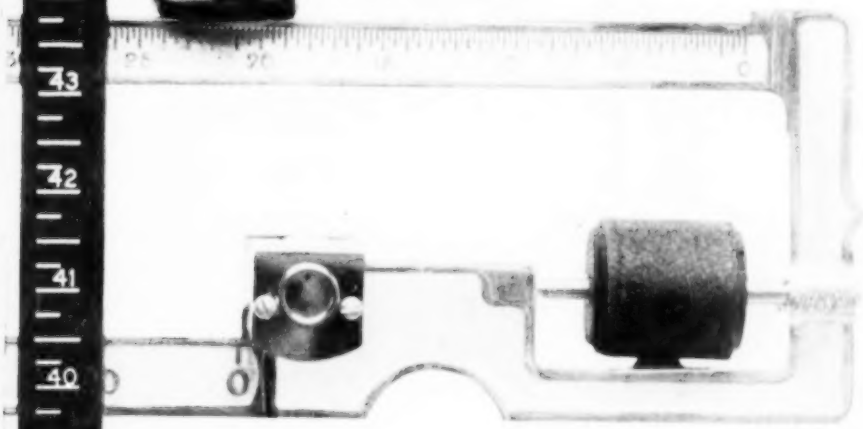

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Prigot, A.; Felix, A. J., and Mullins, S.: Paper presented at the Symposium on Antibacterial Therapy, Michigan and Wayne County Academies of General Practice, Detroit, September 12, 1959 (published Nov. 1959)

*Experimental dosage (see dosage recommendations adjacent)

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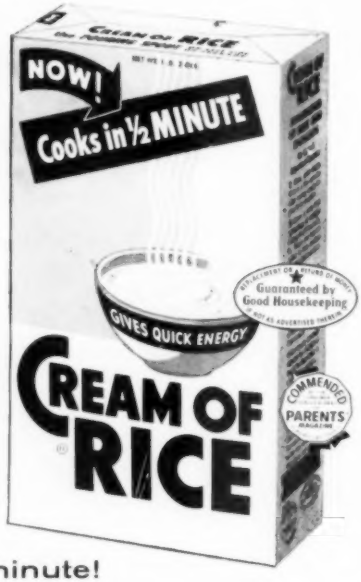


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# THE EDITORS . . .

## Look at Pediatric Progress

*"The times do shift;—each thing his turn doth hold,*
*New things succeed, as former things grow old."*

ROBERT HERRICK – 1591-1634

Indeed, the advances in medicine over the past two decades would seem fantastic to one practicing at the turn of the last century. "New things" continue to appear in such overwhelming array that the impact on the busy pediatrician leaves little time for contemplation of the lessons of the past. Nevertheless, a proper appreciation of our present prophylactic, diagnostic and therapeutic blessings can best be achieved by comparison with "former things."

JOHN FITCH LANDON, M.D.
New York

The following pages present observations of my editorial board colleagues. These views on pediatrics, past, present and future are approached by each editor in a unique way, reflecting his individual background and his own locale experience. Throughout, runs the theme of wonder at the progress which has been achieved.

For your "anniversary number", it seems fitting to record these few observations, calling attention, as others have done in recent years, to some changes in the study of the contagious diseases, particularly in comparison to the emphasis of forty years ago. Then, we were particularly concerned with the care of cases as they occurred, to saving life by symptomatic treatment and to treating or preventing complications. Patients with these diseases were very numerous.

PHILIP M. STIMSON, M.D.
New York

In the summer, there were always several typhoid patients in every medical ward, and New York City had ten thousand cases of diphtheria a year with seven hundred deaths. The Willard Parker Hospital often housed three hundred cases of scarlet fever at one time, the isolation period being thirty days, and the whooping-cough wards were full almost the year around. Nowadays, a practitioner rarely sees a case of whooping-cough except perhaps in a middle-aged adult; typhoid and diphtheria are so unusual, at least in metropolitan hospitals, that medical students rarely can study a case of either; and penicillin cures streptococcus sore throats so quickly that scarlet-fever rash usually has no time to develop and it is quite unusual to hospitalize a case.

Hence emphasis these days has swung to differential diagnosis. A mother reports to a school that her child has "measles" and the school health authorities want to know if this is really so, or could it be rubella, or roseola, or any one of several other diseases. What to do for the other children requires an accurate diagnosis. Measles can still be so serious that correct identification is highly important in order that susceptible contacts can have their possible measles at least modified.

Diphtheria, although approaching extinction in the United States, must not be forgotten when a doctor meets a case of any kind of croup, or of acute laryngo-tracheal bronchitis, or also of so-called neglected quinsy in an old Bowery bum. Chickenpox made malignant by cortisone medication, may act and look almost like smallpox in its severest form.

So-called non-paralytic poliomyelitis now is known usually not to be poliomyelitis but due to a Coxsackie virus or to one of the ECHO group of viruses, and if due to the polio virus it often is found not to be literally non-paralytic, if the patient is carefully evaluated about the tenth day of the illness. Some temporary slight weakness can often be found. The exact viral diagnosis is at the present time not important as far as treatment is concerned, rest being of vital importance in the acute stage in any such case, and no specific cure being available as yet for any of these viruses.

An additional comment might be made about poliomyelitis. In each of 15 of the 28 years from 1915 through 1942, there were less than five thousand cases of poliomyelitis in the United States, that is, less than there have been in either 1957, 1958 or 1959, the years since

we have had the very effective Salk vaccine. While these three years have seen tremendous improvements over the years '48 through '55 (when there were over 25 thousand cases each year) still the gain is not enough, largely because half the population of the United States still has not had three injections of the vaccine. While there is less danger in older adults than in those under 40, there is no magic age limit, and the vaccine now being plentiful, all adults should have three injections and a booster. The injections are harmless, essentially painless and highly protective, although not quite 100 percent. Of course, all adults should get the injections.

The pediatrician in Japan is today facing serious economic difficulties and the young doctors, who are sensitive to the changing world, are choosing other specialties as they feel that they cannot make a living in pediatrics. The hospitals and medical schools are beginning to feel a pinch due to a shortage of trained pediatricians.

YOSHITO NISHIZAWA, M.D.
Japan

The system of specialists has not yet been established in Japan and children are customarily seen by the internist and with the advent of the National Health Insurance System in 1960, the problem will become even more serious. The straits of the pediatrician are due to two outstanding reasons. One is the economic straightjacket of the Health Insurance System and the other is the feeling that there is no special need for pediatric specialists due to the decrease in infectious diseases in children resulting from the introduction of antibiotics. I, however, am very optimistic regarding the latter assumption. The number of patients consulting the pediatrician actually has not decreased. It is only the type of illness that has changed. About 500 years ago, in the time of the feudal warlords, there lived a famous bandit called Goemon Ishikawa. He must have been a charming character as he plays a leading role in a Kabuki play. It is said that he was finally captured and boiled in oil. The credulity of this is not certain but may be true as a popular type of iron bathtub used today is called the "Goemon" tub. Be that as it may be, these poetic lines are attributed to him. . . .

"Though the sands of the beach may disappear
There will always be a thief"

I believe this thought can also be applied to sickness. That is, as long as man is a living organism, there will always be sickness,

"though the sands of the beach may disappear". It cannot be denied that certain bacteria have come under control with the introduction of antibiotics but at the same time, other forms, for example the viruses, have come to the fore and in time, dysentery, pneumonia as well as tuberculosis bacteria, ready for a counterattack, may well be encountered.

Thirty years have passed since I first entered pediatrics and a gradual change has taken place in the illnesses. Diseases which have been considered peculiar to Japan are "Ekiri", "so-called meningitis," infantile beriberi and "infantile" pseudocholera." Of these, the "so-called meningitis" is no longer seen and infantile beriberi is rare but "Ekiri" and "pseudocholera" are still subjects of lively debate. I would like to review these old diseases for the benefit of the young doctors who are unfamiliar with these conditions.

## SO-CALLED MENINGITIS

This condition was first reported in 1901 by Hirota (Professor, Tokyo University) under the title of "Curable Meningitis". It was characterized by vomiting, greenish stools and was followed by meningeal symptoms. It was limited to breast-fed infants of around one year of age and was seen chiefly in the summer. Reports suggestive of this condition are found in the old literature. The "Yoka-koyaku" written by Hojuin Yamashina in 1784 states that chronic "Kyofu" is a condition in which there is vomiting of milk, scanty diarrhea of greenish or blackish mucous stool, swelling of the fontanelle, dilatation of the veins between the eyes and upward rolling of the eyeballs. Erwin Baelz, who taught at the Tokyo Medical School from 1875 to 1900, published a pamphlet "Lehrbuch der Inneren Medizin mit Besonderer Ruckheit auf Japanbearbeitet" in 1900. In this, there is a chapter, Basilar Meningitis, simple and tubercular (especially in children)) and he states that there is a type of non-lethal meningitis which runs a course similar to that of tubercular meningitis but is not serious and the symptoms gradually disappear. Ito (Professor, Kyushu University), presented a paper on the reason for the name "so-called meningitis" at the 30th general session of the Japan Pediatric Society. The term "so-called meningitis" was originated by the pathologists as this was a curable meningitis differing from the tubercular or suppurative. In 1925, Hirai (Professor, Kyoto University) showed clearly by clinical and experimental data, that this was none other than lead poisoning and

the long unknown cause of "so-called meningitis" was finally clarified. This is an outstanding achievement in the history of Japanese medicine. Numerous reports on lead poisoning are found in foreign literature but reports on cases of meningitis due to lead poisoning in infants are few. The use of lead in cosmetics was prohibited in Japan in 1934 and cases of "so-called meningitis" have disappeared completely. In my younger years, cases were observed each year with the coming of June and the hot, humid summer months and diagnosis was relatively easy as the condition was limited to breast-fed infants and the cerebrospinal fluid was a characteristic yellow color. Radiologically too, the typical shadows of lead poisoning were apparent in the ends of the bones. Today, after everything is clear, it seems strange that the cause could not be ascertained sooner. As the use of lead-containing cosmetics came from China over 500 years ago and lead poisoning was common in women, it can be assumed that innumerable infants suffered from the "so-called meningitis" in old Japan.

## INFANTILE BERIBERI

Infantile beriberi is a condition which is almost non-existent in foreign literature so I would like to present a simple review. In 1891, Hirota suggested that infantile beriberi was an independent condition which should be considered separately from nutritional disturbances and in 1897, Miura showed that the pathological changes in the heart of infantile beriberi were identical with the changes in the adult and the two were the same from the pathological standpoint. Clinically, however, the symptoms in the infant differ completely from those in the adult. On the basis of the chief symptoms, infantile beriberi is divided into the heart-failure or cardiac type, the edema type, the paralytic type, the cerebral type and the mixed type. This classification however, is not rigid and the types change readily from one to another. The cause is thiamine deficiency and may be due to ingestion of milk of deficient mothers, or human or cows' milk low in thiamine content. The general symptoms are those of nutritional disturbance and fever. (a) Symptoms of the digestive tract-anorexia vomiting, diarrhea or constipation. (b) Cardiovascular symptoms (cardiac or heart failure type)—cardiac function insufficiency (irregular pulse, tachycardia, increased respiratory rate, palpitation, dyspnoe, cyanosis, moaning, weak heart sounds, systolic murmur, gallop rhythm, foetal heart sound, hepatomegalia, edema, heart failure), hypertrophy of the heart, especially the right-side, drop in blood pressure, audible aortic sound. (c)

Blood picture-neutrophilia, relative lymphopenia, decreased red cell count, reduced hemoglobin, increased thrombocyte count, hydremia, hyperglycemia (cardiac failure stage), increased lactic acid content, decreased catalase level, increased residual nitrogen, increased NaCl (cardiac failure stage). (d) Respiratory signs—irregular respiration, fixation in thoracic respiration position, apnoeic attacks, respiratory standstill, paralysis of the diaphragm. (e) Edema—decreased urinary excretion, edema. (f) Nervous system manifestations (paralytic type)—weak cry, hoarseness, loss of voice, inspiratory wheeze, ptosis of the eyelids, changes in the ocular fundus (axial neuritis), heightened, weak or absent patellar reflex. (g) Cerebral signs—excitation, jerking spasms, convulsions, trembling of the extremities, strabismus, upward rolling of the eyeballs, nystagmus, loss of interest, apathy, loss of facial expression, coma. Numerous infants, 3-6 months of age, died showing these symptoms.

In the past 10 years however, cases are encountered so rarely that it is difficult to obtain cases for teaching purposes. My colleagues at other institutions also report a lack of cases. The statistics of the Ministry of Health and Welfare however, show that infantile beriberi ranks third in causes of infant deaths. This may be due to the convenience in giving beriberi as the cause of death because of the resignation of most of the mothers to this diagnosis but on the other hand, there may still be cases in the rural districts. The term "Kakke" (beriberi) came from China and it is already encountered in the literature of Japan as early as the 17th century. The people of Japan started eating polished white rice at about this time and it can be assumed that beriberi became prevalent at the same time. Tokyo was then known as Edo and beriberi was called "Edo sickness" in eastern Japan while in the western parts, it was called the "swelling sickness". For the Japanese who have suffered from this condition for several hundreds of years, infantile beriberi is a hated condition with bitter memories.

## "EKIRI"

I do not agree with the belief that "Ekiri" and the later described "pseudocholera" are conditions peculiar to Japanese children; only the terminology is unique. "Ekiri" was first described as an independent infectious disease of childhood by Ito in 1898. He based his assumption on clinical, pathological and bacteriological studies on a pathogen (a coliform bacillus) isolated from patients in the Fukuoka district. Today, 60 years after it was first reported, the etiology and mechanism of development of "Ekiri" are still subjects of heated dis-

cussion. To an outsider, this appears almost ridiculous. The problem of "Ekiri" was taken up by a research group from the United States in 1947 and it was said that the symptoms were those of incidental tetany resulting from hypocalcemia but I will not take it up here as much has been written on this. "Ekiri" appears to have been present from ancient times and it was called "Hayate" "Taifu" or "Kyusho", all meaning sudden death. As the causal organism of dysentery was not yet known, it is not strange that Ito isolated a coliform bacillus and considered this to be the pathogen. In 1921, Ohara, who studied under Ito, succeeded in isolating a new pathogen which he called the Ohara bacillus. Shigella however, has been isolated from the stool of "Ekiri" patients and I do not believe that it is necessary to differentiate between "Ekiri" and dysentery. I have always considered "Ekiri" and dysentery as one but as I do not have sufficient evidence or knowledge to support this, I will not attempt to discuss it here. The various theories on "Ekiri" are as follows.

1. Essential "Ekiri" Theory
Minoda suggests that as long as the pathogenicity of E. coli cannot be denied, "Ekiri" should be considered as fulminating colitis due to E. coli.

2. "Ekiri" Syndrome Theory
The toxic symptoms are suggested to be due to bacterial infection but not to a direct action of bacterial toxin and the presence of other important causal factors is essential.

3. Theory that "Ekiri" and Dysentery are the same

4. Ohara Bacillus Theory

According to this theory, "Ekiri" is caused by the Ohara bacillus and even though clinical symptoms, course and pathological changes may be alike, the condition should be considered separately if the causal agent differs.

In 1954, a committee for investigating "Ekiri" was set up by the Ministry of Health and Welfare and "Ekiri" was defined as follows:

"Ekiri" is a general diagnosis to designate a fulminating type of dysentery which is characterized by high fever, nervous disturbance (clouding of consciousness, convulsions), circulatory disturbance (tachycardia, weak pulse, pallor, cyanosis, coldness of the extremi-

ties), digestive tract disturbance (diarrhea, bloody mucous stool, vomiting, nausea) and an extremely short course.

Dysentery cases taking a similar course are no doubt encountered throughout the world and I do not believe that the term "Ekiri" is necessary. It is also my opinion that the hypocalcemia is a secondary change and not primary.

### PSEUDOCHOLERA INFANTUM

Even to those who are familiar with infantile beriberi and "Ekiri", the term "pseudocholera" may be puzzling. Ito (Professor, Kyusho University), appears to have liked to name diseases. He not only named "Ekiri" and "so-called meningitis" but is also the author of the term "pseudocholera infantum" (1906). This is an acute diarrhea with vomiting occurring in breast-fed infants from late autumn to early winter and is characterized by the passage of ricewater-like, whitish, watery stool. The term was given to the condition from the similarity of the symptoms to "Intoxication Cholera Infantum" occurring in cows' milk fed infants in the summertime. The condition appears to be very serious because of the severe vomiting, diarrhea and dehydration but the prognosis is always good and the patient recovers within several days. Ito stated that the cause was unknown and even today, there is no accepted theory as to the cause. This subject is always taken up at each meeting of the Japan Pediatric Society and in April 1959, a symposium was conducted on this condition at the general meeting under my chairmanship. Five hours of discussion failed to give a satisfactory conclusion and an agreement could not be reached even in regard to a proper name. The following is an excerpt from the records of the symposium:

"The name of this condition is a source of trouble. As you can see, all three speakers have used differing names (Pseudocholera infantum, White diarrhea, Diarrhea with white stool). It would not be at all surprising if doctors, other than members of this Society, considered these to be three different conditions. Besides these three, there are eight other names in the literature. This is not only a cause of misunderstanding among doctors and the Health Centers, but will hamper medical education. As this was a very fine opportunity, a letter was sent to the leading members of the Society in an attempt to obtain uniformity in the nomenclature but instead of getting one good suggestion, twelve other names, making twenty in all, were suggested. From the fact that there were so many names and

differing theories regarding the cause, I personally visited the various investigators with the idea that there may be more than one disease but in my opinion, the patients were all suffering from the same illness. It is unnecessary of course to name the place, but it is reported that the Health Center of a certain town had a good scare because of the term "cholera". How difficult a task it is to change a notion"!

The problem has been made more difficult by the various theories as to the cause. For example, the grippe theory, the syndrome theory, the virus theory, the constitution theory, etc.; and discussion is out of the question for a non-specialist as I. If any of the readers happen to have experienced cases similar to this, I would appreciate information as I do not believe that this condition is peculiar to Japan.

In closing, it is above all, my hope that these observations may invite an exchange of views by fellow-pediatricians.

The present most interesting aspect of our experiences in pediatric practice here in Denmark is the changing nature of the patient requiring acute or emergency cure.

P. W. BRAESTRUP, M.D.
Denmark

Of course, in a public pediatric service which admits 2000 in-patients annually for treatment (on request chiefly by general practitioners), we still see the "acute" patient with a severe gastroenteritis, a neonatal respiratory distress, the precomatic or comatous diabetic, or a desperate septicemic condition. But thanks to the better general medical care and routine health examinations with advice regarding general hygiene and nutrition, these are becoming more and more rare. Thanks also to effective antibiotic and better routine laboratory guidance in fluid therapy, they are better controlled, and lessen the problems for the staff.

Attention appears to be shifting to the child in acute mental distress. This represents the girl or boy in conflict with home or school conditions—the young person who feels to a keen extent, insecure in his surroundings. There is no effective drug to cure him immediately—no psychiatric or child guidance service to ease his problem without the drastic removal from home atmosphere. All are quantitatively lacking, and unfortunately, this situation

does not seem to be correcting itself. Moreover, those in charge seem unable to perform with the necessary speed needed in situations of great stress.

An increasing number of this type of patient is evidencing itself in our pediatric services. Child welfare organizations are working hard to help—particularly through the establishment of "small private homes" for short-time observations before further treatment or placement is required. But there is still much to be done in the development of facilities and their availability for these children.

For the past ten or fifteen years pediatric principals in this country have called on psychologists to assist in the treatment of these children. They have guided nurses, educators and others in the special work required for the care of severe mental or behaviour disturbances.

In sending you my views on some significant development in the field of pediatrics, I would like to refer to a subject which is difficult to evaluate in the form of figures or statistics, but which I am sure is at the back of pediatricians' minds. So let me go from the field of statistics, drugs, etc., to some observations which lead to "pondering over".

RONALD N. MACLEAN, M.D.
Argentina

I refer to the influence on the infant of deep anesthesia and low prophylactic forceps during delivery versus the Reed method of painless childbirth. In many countries, painless childbirth is becoming popular because the obstetricians prove their good results, how the expectant mother prepares her mind to deliver the baby with a lower margin of pain.

The obstetricians have taken sides on deliveries with or without deep anesthesia. How about the *pediatricians?* No one can deny that an infant born without anesthesia cries more lustily at birth and has a better color. Whatever the advantages from the mother's or the obstetrician's point of view, the infants born by a routine procedure of low prophylactic forceps with deep anesthesia seem to be "born asleep" and remain lethargic for some time, but gradually they get rid of the anesthetic and are sent home in a few days in perfect condition.

Could that anesthesia or slight cyanosis have affected the infant so that he will be less intelligent than he might have been? Are there any "unknown cause" statistics comparing those born without, and with anesthesia and low prophylactic forceps?

The important question is whether the rhythm, speed outlook of our modern times should be changed for the welfare of children. There is no doubt that painless childbirth means more patience and work from the mother's and obstetrician's point of view.

I hope readers will ventilate their opinions on the subject, as I feel this important point in pediatrics should not be overlooked.

MICHAEL A. BRESCIA, M.D.
New York

We are constantly learning new methods and unraveling slowly but surely, *pari passu*, the advances in the basic sciences, the complexities of the human body. This is progress without which any field would deteriorate and finally become extinct, having lost its raison d'être. Pediatrics being a comparatively young but vigorous specialty had had its fair share of advances . . . the most outstanding which come readily to mind are: 1. The importance of the enzyme systems together with their relationships to metabolic and other disorders, e.g., phenylketonuria with emphasis on its early recognition by the simple ferric chloride "diaper test" as a screening device and thus possibly truncating the development of a mental retardate. 2. The physiological explanation for the development of jaundice in the newborn, either so-called physiologic or pathologic in the blood incompatibilities being due to an early deficiency in the appropriate enzymes to effect a change of bilirubin in conjunction with glucuronic acid from the indirect or unconjugated (toxic to cells of the nervous system) to direct or conjugated (non-toxic) type then readily excreted. The therapeutic implication is the possible development of an enzyme which can be used in the early days of life to substitute for this early deficiency. The effectiveness of such an enzyme might obviate the need for exchange transfusions and also minimize further the incidence of kernicterus. 3. The daring of surgery in and around the heart to correct the protean cardiac anomalies cannot fail continually to be a source of astonishment. The intrepidness of these surgeons was recently exemplified by a new procedure for the alleviation of

transposition of the great vessels in which the superior vena cava was anastomosed directly to the right pulmonary artery.

A new avenue of advance for pediatrics is on the horizon in the production of a "Blood Pressure Follower" which was developed by Dr. J. H. Green of London. There are no accurate figures of blood pressures in infants and certainly none in the newborn. Can one imagine the information which would be made available if there were an instrument which could easily record the blood pressure of a newborn the instant of birth, the changes that might take place after the cord stops pulsating and then tied? The possibilities of accurate blood pressure estimations in infants are limitless. Such an instrument has been developed and made practicable by the utilization of a special cuff which has been designed to enclose an entire finger. The arterial pulsation from the digital artery of a finger is picked up by a piezo-electric crystal placed over the artery. This pulsation is employed to open an air-valve which inflates the finger cuff from a small pump in the apparatus. The cuff occludes the artery proximally to the point of application of the crystal, and when this occlusion is complete, the air-valve is closed and a leak allows the cuff to deflate until pulsations reappear when further air enters the cuff. The apparatus thus maintains the cuff at the same pressure as that in the digital artery. The blood pressure is recorded on a moving chart resulting in a visual and permanent record.

These are a few of the many important advances that have materialized. However, they are illustrative of what can and has been accomplished. The blood pressure studies as indicated can be one of the many new avenues to be opened in the near future.

It seems to me that just as short a time as ten years ago, a pediatrician had first to be able to get along with children . . . then with the parents, and then to be referee between the child and the parents. That was when the child was doing his mischief normally! Discipline by the wood-shed was tabooed. "Don't hurt the child's psyche" was encouraged. Now the pendulum seems to be swinging into a more neutral position.

CATHERINE E. SPEARS, M.D.
New Jersey

The most interesting advance, to me (in my dedication to pediatric neurology), is how important the nervous system is becoming. Ten years ago, pediatricians referred any problem that seemed to be primarily a defect of the nervous system to the Neurologist or Neurosurgeon. Today, the pediatrician is active as coordinator of the team of physicians planning and carrying out the rehabilitation of the handicapped child—whether it be a physical, mental, or emotional handicap.

I do wish that the future might see more time alloted to pediatricians so that they could evaluate the whole child, instead of being put in the position of having to treat children with routine colds, etc., on a "volume" basis. When this happens, all too little time is found to devote to the lengthy, more serious problems which, as I say, are essential for making appraisals on a *total* basis.

**HERBERT V. VON GAL**
**Connecticut**

Probably one of the most dramatic developments in Pediatrics over the past few years has been the surgical treatment of congenital cardiac conditions. Few medical or surgical procedures give more striking results than cardiac surgery. It is a wonderful thing to see a cardiac cripple become a normal healthy child. Most all of these advances in cardiac surgery have been dependent on or at least greatly helped by the precise anatomical evaluation of the congenital defect by angiocardiography prior to cardiac surgery.

Congenital defects such as tracheo-esophageal fistulae, imperforate ani, atresias of segments of bowel, absence of the diaphragms and other such abnormalities that may lead to death of an infant in a few hours or days all are greatly dependent upon the improved x-ray evidence of the abnormality, its localization and extent prior to the surgery. It is now a rather common procedure in a child with an intussusception to have not only the diagnosis of this abnormality confirmed by x-ray but also to have it reduced under the fluoroscopic control of the barium enema.

These are all rather dramatic emergency situations but the more routine x-rays of infants and children are still essential to the proper diagnosis and treatment of many more common diseases.

# Impaired or Absent Fundus Reflex in Infants and Children

*(With especial reference to Obstruction by Cataract)*

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Normally the pupillary area of the eye, which is black when viewed by direct light, presents a red fundus reflex when a beam of light from the ophthalmoscope is directed at it from a distance of 20 inches or so, with no lens before the peephole in the ophthalmoscope.

Many conditions which may obstruct the fundus reflex in the eyes of newborn infants and of children are peculiar to the young, some resemble those in adults because, in contradistinction to organs in other parts of the body, the eyes of the newborn are approximately 75 per cent developed at birth and are almost fully grown at 2 years.

That the red fundus reflex seen with the ophthalmoscope is impaired or absent may be observed by the pediatrician during his routine examination or his attention may be directed primarily to the patient's eye, or eyes, by the parents or guardians who happened to notice, or think that they noticed, something abnormal about the appearance of the "black part" of the eye.

Although infants' eyes are difficult to examine, evaluation of the history and of the mental and physical development of the patient may provide clues which, together with the findings accumulated by careful observation and by repeated painstaking attempts at examination, help the pediatrician to arrive at a diagnosis.

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AIDS TO EXAMINATION

If abnormal conditions are detected or suspected, examination should be facilitated by dilating the pupil, using special types of illumination such as direct focal illumination, (with the aid of a loupe for magnification—Figs. 1 and 2), the use of the ophthalmoscope, and provided that there are no contraindications, even general anesthesia. Full dilation of the pupil may be obtained by instillation of cyclogyl 1%, homatropine 1%, or neosynephrine 10%, and, if desired, their mydriatic effect may be neutralized by 1% pilocarpine hydrochloride solution.

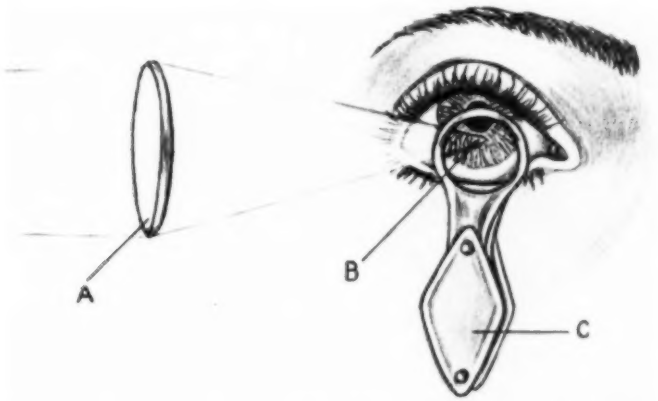


Fig. 1. Schematic representation of focal illumination using condensing lens and loupe (clinical view). (A) condensing lens perpendicular to source of light; (B) apex of the cone of light focused on the part of the eye being examined—the iris—studied under magnification by means of (C) a 10 X loupe.

Many opacities can be examined in detail by rotating a + 10.00 D. or a + 12.00 D. lens into place before the aperture in the ophthalmoscope held close to the patient's eye and tilting the instrument slightly from side to side or up and down during the inspection of the lens.

Parallactic displacement by ophthalmoscopy may be utilized to determine whether an opacity is situated in the anterior or in the posterior part of the lens. The former appears to move in a direction opposite to the direction of movement of the eye of the examiner, the latter appears to move in the same direction as the movement of the eye of the examiner.

Having ascertained that the cornea, the anterior 1/6 of the outer coat of the eye, is clear and transparent and therefore is not responsible for obstruction to the red fundus reflex, the examiner proceeds to scrutinize the deeper areas and tissues—the anterior chamber, the iris, and the pupillary area, for any possible condition which may account for a partial or complete absence of the usual red fundus reflex.

If the iris and its opening (the pupil) are visible, the examiner should note the number of pupillary openings present and the position, the shape, the size, equality and reactions of the pupil.

If the pupillary area is obstructed, he should determine the cause of the obstruction and whether the obstruction is partial or complete.

Fig. 2. Focal illumination using light bulb from ophthalmoscope with aid of 10 X loupe.

More than one opening in the iris, each with its own sphincter, (true polycoria) is a very rare condition. Surgical or traumatic holes in the iris and those associated with coloboma of the iris or with separation of the iris from its root (iridodialysis) are more common.

Instead of the normal slightly inferonasal location of the pupillary opening, a peripherally situated opening may be present (corectopia). Normally, the pupils are practically circular but disturbances in shape (dyscoria) may be present. They may be oval, rectangular, slit—, pear—, or hourglass-shaped.

Normally, the pupil measures from 2.5 to 4 mm. Large pupils occur in psychic or cervical sympathetic stimulation, third nerve paralysis, trauma, glaucoma, and as a result of drugs. Small pupils occur in third nerve stimulation, in reaction to light and to accommodation-convergence, in sympathetic nerve paralysis, in iritis, and as a result of drugs.

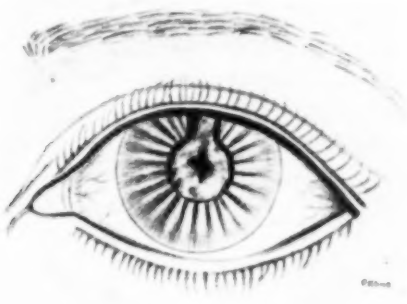

Fig. 3. Secondary or after-cataract (following extracapsular extraction of lens).

The pupillary area may be partly or completely obstructed by a persistent pupillary membrane, an organized inflammatory exudate, a secondary membrane (Fig. 3), blood, a purulent or fibrinous exudate, a cyst or tumor in the anterior chamber, glioma of the retina, or the presence of an opacity (cataract).

A persistent pupillary membrane may be manifested as a strand of iris tissue across the pupillary opening or ending freely in the anterior chamber.

An organized inflammatory exudate appears as a gray membrane (associated with iridocyclitis) occluding the pupil.

A secondary membrane may follow extracapsular cataract extraction. It is formed by remains of lens or of lens capsule and organization and proliferation of the cells of the lens. Blood in the

anterior chamber (hyphema) may follow trauma or surgical procedures. It may absorb rapidly or remain for a long time and may require surgical removal if secondary glaucoma ensues.

A fibrinous exudate may present a gray coagulated transparent mass in the anterior chamber.

A purulent exudate may appear as a very small, scarcely visible crescent at the bottom of the anterior chamber or it may fill it entirely.

A cyst of the iris, an inflammatory or immigration cyst may partially or completely fill the anterior chamber.

A tumor of the iris or of the ciliary body may appear as a brown pigmented mass obstructing the pupillary opening.

Glioma may appear as a yellowish mass filling the eyeball and obstructing the pupillary area.

If these conditions are absent, all parts of the *lens* should be examined through the fully dilated pupil.

An opacity in the lens, although white or gray when viewed by direct light, will appear black against a red background when viewed with the ophthalmoscope, (a method actually comparable to retro-illumination or transillumination) just as a piece of white chalk will appear black when placed against a white light, such as an electric bulb.

The normal crystalline lens is invisible under illumination by natural or artificial daylight, or by light from the ophthalmoscope, because it is transparent. (It fluoresces under red-free light.) It is visible when it becomes translucent or opaque as a result of partial or total opacification (cataract).

Normally, the crystalline lens, a biconvex disk, about 8 mm. in diameter, rests on the anterior face of the vitreous suspended from the ciliary processes by strands of the zonular ligament. Even before birth, part of the lens, the fetal nucleus, is already formed. This nucleus is limited anteriorly by a suture arranged like an erect Y and posteriorly by a suture arranged like an inverted Y. Postnatally, as the lens develops, fresh layers of fibers are successively formed from the equatorial part of the epithelial cells behind the anterior capsule so that instead of being shed, (like other ectodermal structures— skin, hair, nails) the lens fibers are crowded together in an onion-like structural arrangement to form the lens.

CONDITIONS OF THE LENS OTHER THAN CATARACT

In addition to opacification, the possible presence of any of the following conditions of the lens should be noted: Absence of the lens, the position of the lens, and the presence of pigment or of adhesions.

Absence of the lens (aphakia) may be congenital, traumatic, or surgical (following cataract extraction). In aphakia, the anterior chamber is deep, the iris is tremulous (iridodonesis) and the fundus details viewed ophthalmoscopically appear in miniature.

The lens may occupy its normal place, be partly out of the pupillary area (subluxated Fig. 4), or completely out of the pupillary area (dislocated). Dislocation may be congenital, traumatic, or the result of high myopia or of buphthalmos. The lens may be dislocated under the conjunctiva, into the anterior chamber or into the vitreous.

Stellate, or tripolar brown pigment spots on the anterior capsule of the lens, Fig. 5, may be congenital, the result of retained iron in the eyeball (siderosis), or, when arranged in the form of a circle, may represent permanent evidence of adhesions from an old iritis which formed when the pupil was contracted.

Adhesions between the lens capsule and the iris (posterior synechiae) frequently occur in iritis. An organized exudate may also be present in the pupillary area (in iridocyclitis).

CATARACTS—PROGRESSIVE OF STATIONARY?

It is unfortunate that the term "cataract" is generally applied to all types of opacities of the lens because in the layman's mind this term is often synonymous with imminent loss of sight and with total blindness. It would be preferable to invent one term for the stationary (or relatively stationary) type of cataract and another term for the progressive type of opacity of the lens.

Although, in many cases, it is difficult to predict the rate of progress of an opacity, it is important to be able to distinguish between opacities that are stationary and those that art progressive Figs. 6 & 7 (and eventually result in opacification of the entire lines).

Stationary cataracts include the anterior capsular, Fig. 8 the anterior polar, coronary, some types of lamellar (or zonular), some types of posterior polar, posterior capsular and the punctate catar-

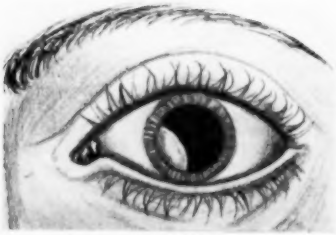

Fig. 4. Subluxated lens. Note opacity partly obstructing pupillary area.

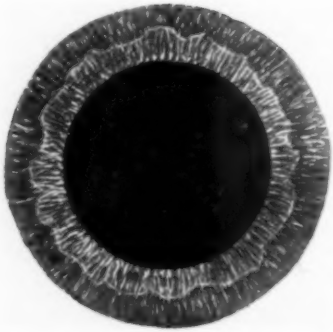

Fig. 5. Congenital pigment on anterior lens capsule.

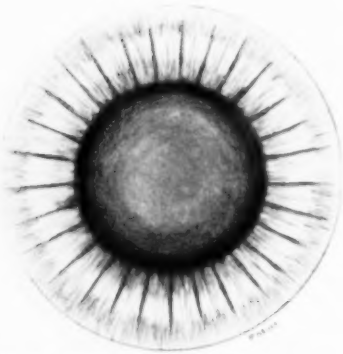

Fig. 6. Progressive (nuclear) cataract. Note opacity at center of lens.

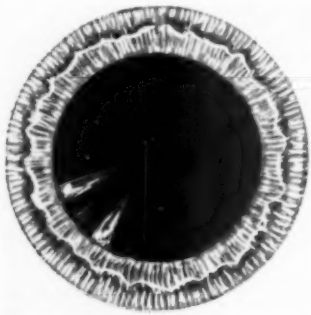

Fig. 7. Progressive (cortical) cataract; early stage. Note wedge-shaped opacities ("spokes" or "riders") at periphery.

acta cerulea. Sharply demarcated opacities, both when composed of a number of discrete spots or dots or even when uniform in composition, are generally stationary, while opacities that appear to be poorly demarcated, soft and fluffy, are more liable to be progressive.

The location of anterior and posterior capsular Fig. 9 and polar cataracts is self-descriptive. The lamellar (or zonular) cataracts Fig. 10 are situated between relatively clear areas of lens fibers. They develop in childhood as a result of malnutrition, high fever and convulsions. Coronary cataract Fig. 11-A which develops at pub-

erty presents rounded or club-shaped opacities at the equator in the anterior and posterior cortex of the lens. Cataract cerulea Fig. 11-B consists of punctate bluish opacities.

### CATARACTS—ONSET AND DEVELOPMENT

In regard to the time of onset and development of an opacity in the lens, it might be pointed out that some cataracts are congenital, others are acquired, although both types may be hereditary or present familial tendencies. Acquired cataract is associated with local conditions or with general conditions.

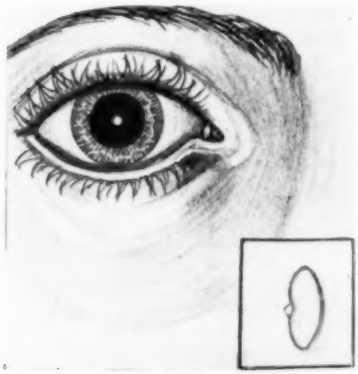

Fig. 8. Anterior capsular cataract. Inset shows position of opacity in cross-section.

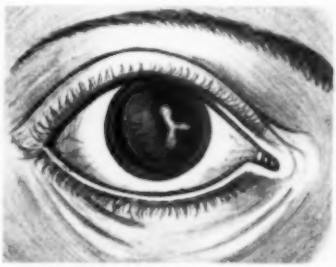

Fig. 9. Subcapsular cataract (in a subluxated lens)—front view.

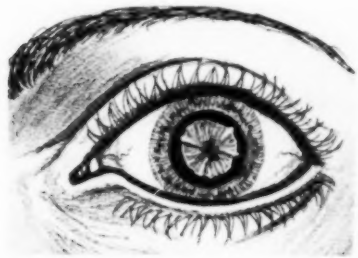

Fig. 10. Zonular or lamellar cataract. Opacity situated between clear lens fibers.

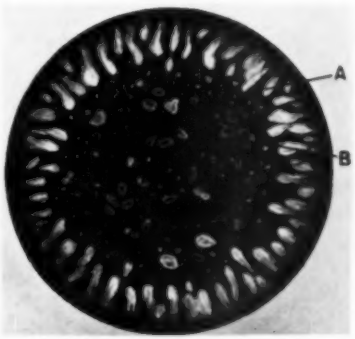


Fig. 11. (A) Coronary cataract at periphery of lens. (B) Cerulean cataract.

CATARACT—LOCAL CAUSES

Among the local causes are direct and indirect trauma including perforated and non-perforating trauma or keratitis, X-rays, radium, ultra-violet and infra-red light; and inflammatory or pathologic changes in the iris, ciliary body, choroid, retina and vitreous (such as high myopia, detachment of the retina, intraocular inflammation, parasites and absolute glaucoma). Most of these are called complicated cataract and are generally characterized by the formation of a rosette or stellate opacity in the posterior, or less commonly, in the anterior cortex of the lens. A rosette opacity Fig. 11 may be stationary or progressive. In early cases of retinitis pigmentosa, granular subcapsular opacities may be seen at the posterior pole of the lens.

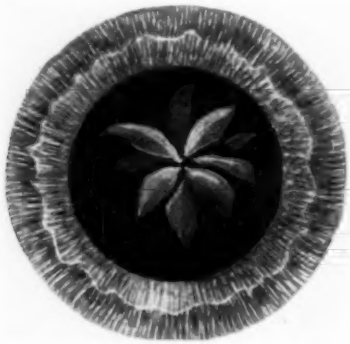

Fig. 12. Rosette cataract. Note distinctive arrangement of opacities.

CATARACTS—TRAUMATIC

In some cases, trauma may occur in combination with the presence of other factors to produce a cataract. Differential diagnosis may also be important from a medicolegal aspect. Because children are particularly susceptible to this type of cataract, it is worth while discussing this condition in greater detail.

In a perforating eye injury, when the capsule of the lens is ruptured, the cortical fibers become swollen and opaque. The proteolytic action of the enzymes of the aqueous breaks down the swollen lens fibers and effect their disappearance. Through the opening in the lens capsule, the entire lens (except for the capsule) becomes absorbed.

This process will occur only in patients under 25 years of age. After this age, a hard nucleus has formed which cannot be absorbed so that surgical removal is necessary.

The proteolytic process may occur without much reaction (just as after a surgical discission of a cataract in the eye of a child) or it may be accompanied by an intense reaction. The reaction may occur independently or it may be accompanied by an increase in the intra-ocular pressure (glaucoma). The latter results if the swollen lens fibers block the angle of the anterior chamber (through which filtration of the aqueous normally occurs). Tension may also result from vasomotor disturbances sometimes associated with trauma.

If glaucoma occurs, the swollen lens fibers may have to be evacuated from the anterior chamber by the method used for extraction of cataract in adults. In young children, absorption may occur in approximately 4 weeks, in older children in from 6 to 8 weeks, provided that the capsule remains wide open.

If the opening in the capsule heals and seals off the cataract, absorption cannot continue. The cortical remains will have to be evacuated by another operation (linear extraction) which should preferably be performed no sooner than six months after the injury.

Traumatic cataracts may also occur in non-perforating injuries such as contusions. A posterior Fig. 12 rosette (and occasionally an anterior stellate opacity) may develop in from a few hours to a few days following the injury and the opacity may clear up in a few days, remain stationary, or progress to involve the entire lens.

A child's eye is particularly sensitive to radiation. Vitamin C and calcium are required to maintain transparency of the lens (lamellar cataract occurs in association with dental hypoplasia).

### CATARACT—GENERAL CAUSES

Among the general causes are diabetes; faulty diet (malnutrition, fever); endocrine disturbances (tetany from parathyroid deficiency, cretinism; dermatologic conditions (neurodermatitis); and toxemia (diphtheria, nephritis, malaria, poisons and maternal rubella).

In order to determine the etiology of a cataract in a child, knowledge is required not only of the condition of the eye proper but also of the body in general. As pointed out, the transparency of

the lens can be maintained only as long as the capsule remains intact and certain specific essential materials are supplied to it in proper concentrations. Therefore, many hereditary, as well as many physico-chemical factors of metabolism of the crystalline lens must be considered.

Grayish-white flaky opacities in the anterior and more frequently in the posterior subcapsular cortex occur in diabetes. These opacities are usually bilateral and generally progress to complete opacification of the entire lens in a short period of time. The postoperative visual result is dependent on the degree of damage in the retina, especially at the macular area, caused by the diabetic condition.

In juvenile diabetes, the lens may become milky-white within a few days as a result of the formation and coalescence of a great number of white dots along with water clefts.

The type of cataract which develops during a period of malnutrition or of fever in childhood is typically lamellar (zonular Fig. 10) as has already been mentioned.

Cataracts of endocrine origin deserve additional emphasis: Cataract in association with mongolism and cretinism have been mentioned. Anterior and posterior subcapsular punctate opacities and/or perinuclear opacities which occur in these conditions are stationary and usually not sufficiently dense to require surgical interference.

An irregular elevated thickening of the anterior subcapsular layers of the cortex may occur in neurodermatitis of young adults. Opacities of this kind are frequently bilateral and progressive and therefore require surgical intervention when sufficiently obstructive to vision.

Maternal rubella acquired during the first trimester of pregnancy may result in cataract in the offspring (often associated with other anomalies such as deafness and cardiac affections).

### FACTORS TO BE CONSIDERED IN REGARD TO SURGICAL INTERVENTION

Surgical intervention depends on how much an opacity interferes with vision, whether the opacity is stationary or progressive, and on the general state of the patient. It also depends on whether only one or both eyes are affected.

Whether the cataract is congenital or acquired, operation is indicated if its size or site is such that it obstructs the greater part of the pupillary area and/or its density is sufficient to interfere with vision. Anterior polar cataracts are less obstructive to vision than are posterior polar cataracts. In infants, the amount of vision present can only be estimated by the extent of obstruction of the red rundus reflex.

Whether a relatively non-obstructive cataract is stationary or progressive is also a determining factor.

Lamellar cataracts vary in density and therefore in the degree of obstruction to vision and may or may not require surgical treatment. Because they occur as a result of tetany or convulsions in infancy, attention directed to proper control of calcium metabolism may be helpful in preventing their onset and development.

Moreover, the general state of the patient must be considered before subjecting an infant to surgery under general anesthesia.

Operation should be advised between the ages of 3 and 6 months to allow the rods and cones in the retina (Fig. 00) to develop properly by exposing them to stimulation by light.

Even in cases of unilateral cataract, although both eyes cannot be used together as a pair postoperatively, surgery should be recommended early in life, for the earlier the retina is exposed to light, the better is the prognosis. Vision in the operated (aphakic) eye then can be stimulated by occlusion of the non-operated eye (with an approximately + 10.00 D sphere) at periodic intervals, while the proper correction is worn before the aphakic eye.

### SURGICAL TREATMENT OF CATARACTS IN INFANTS AND CHILDREN

Discission is the process indicated in cases of congenital, immature, or mature cataracts in patients under 25 years of age. Instead of the old method of needling which in most cases had to be repeated a number of times, a better opening can be obtained by a through-and-through V-shaped opening in the capsule and lens.

After the pupil is fully dilated, a Ziegler knife-needle applied to the upper limbus, is introduced into the anterior chamber and directed so that it rests at a point on the anterior capsule just within the lower margin of the iris and about 3 mm. temporal to the vertical midline. The point is then thrust into and through the whole thickness of the lens and, with a sawing motion, a cut is made up-

ward and nasally toward the point of incision and up to the upper margin of the pupil. The knife-needle is then withdrawn from the lens but not from the anterior chamber. It is re-directed to a point corresponding to the first puncture, but on the nasal side of the vertical line and the procedure is repeated so that this incision meets the first to form a "V". The instrument is then withdrawn from the eye.

A different procedure preferred by some surgeons consists of using a keratome to make an incision slightly within the limbus, entering the anterior chamber and penetrating the anterior capsule of the lens so that much of the lens substance can be expressed through a wide opening in the capsule, and the anterior chamber can be irrigated free from lens substance. Absorption is more rapid when this procedure is followed and useful vision is obtained in a shorter time.

### HISTORY OF CATARACT

The history of cataract is interesting. It extends backward about at least 3,000 years. The earliest record is in a treatise by Susruta of ancient India, who recognized cataract as an opacity of the lens and described many varieties in detail along with his technique of its treatment by couching.

Somehow this learning of the Far East was forgotten, for the subsequent history of cataract is replete with prejudice and fantasy.

The first classical teachings of Celsus (25 B.C.-A.D. 50) assumed that cataract was a corrupt inspissated humor (accumulated in the space between the pupil and the lens) which obstructed the visual spirits. Sight could be restored by displacing it or by breaking it up with a needle. The Greek writers maintained this view (Galen 131-210) and much later in spite of Kepler (1571-1630) who demonstrated that the lens was not the essential organ of vision.

In spite of Quarré (1643) who like the ancient Hindus viewed cataract as an opacification of the lens and in spite of Rolfinck (1656) and Maitre-Jan (end of 17th Century) who demonstrated that the material displaced in couching was not a thin membrane but a thick rounded body, it was not until Brisseau (1705) that doubt was thrown on the theory of humoral pathology.

Daviel (1748) published an account of the extraction procedure, instead of the displacement method, of a cataractous lens. But the

extraction method survived for only a short time and popularity returned to the older procedure of couching. It was not until about 100 years later that extraction was finally accepted as the procedure of choice for cataracts of adults over 25 years of age.


## SUMMARY

The pediatrician is fully aware that the pupillary area normally presents a red fundus reflex but what possibilities should he consider when he is confronted with an infant or child whose eye (or eyes) reveals an impairment or absence of this reflex?

Having excluded such possible causes of obstruction as affections of the cornea, abnormal contents of the anterior chamber, and affections of the iris, he should direct especial attention toward cataract as one of the chief possibilities.

It is pointed out that a partial or complete cataract appears black against a red background when examined ophthalmoscopically (because the opacity is then retroilluminated) just as a piece of white chalk appears black when held against a bright light.

After careful examination of the opacity, an attempt should be made to ascertain whether the opacity is unilateral or bilateral, in what part of the lens it is located, whether it is developmental or acquired, how obstructive it is, and whether it is stationary or progressive.

Early surgical intervention is advocated to remove the obstruction so that the retina will be exposed to stimulation by light, for this is the only way that the retina can be given an opportunity to develop.

The ancient concepts of cataract and its surgical treatment are described for comparison and contrast with the modern surgical procedures for the treatment of cataract in infants and children.


Illustrations from Berens and Zuckerman "Diagnostic Examination of the Eye", and "Perimetry" by Zuckerman, courtesy of J. B. Lippincott Company, Philadelphia, Pa.

*875 Park Avenue, New York 21, N. Y.*

# A New Treatment of Upper Respiratory Infections with Trypsin-Phenylephrine Nose Drops***

Anthony J. Maffia, M.D.* and Morrison Levbarg, M.D.**
Louis A. Perillo, M.D.** and William Greenberg, M.D.**

Nasal medication has been used since the year 1880. The use of oily sprays and vapors of various colors and odors was followed by Dowling packs. It was not, however, until 1926 when Chen[1] introduced ephedrine that nasal medication came of age. Since that time many sympathomimetic drugs, chemotherapeutic agents, antibiotics, antihistamines and hormones have been used in various combinations. All of these have definite shortcomings and laboratory research and controlled clinical studies on the value or even the safety of these drugs is by no means complete. Ephedrine, for instance, has a diminishing responsiveness to successive doses. Naphozoline[2,3] may cause drowsiness and is particularly apt to cause rebound phenomena.

It is generally accepted that most acute upper respiratory infections are of viral origin. Antibiotics[4] and chemotherapeutic agents are not of value as therapeutic agents except possibly in those instances when the large sized viruses, e.g., psittacosis-lymphogranuloma venereum are present. If secondary bacterial invaders play a significant role, it is still doubtful that local antibiotics should be employed.

Careful evaluation of antihistamines shows many of the original claims for these drugs not to be valid. They do appear to exert some local anesthetic action and most antihistamines are weakly parasympatholytic resulting in an atrophine-like effect, e.g., drying of mucous membranes.

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Recently the adrenal steroids have been incorporated in nasal preparations because of their anti-inflammatory action. Considerably more experience is needed to properly evaluate this use of steroids and caution must be exercised when employing such potent drugs.

The use of nasal medication should be predicated on the cellular structure and function of the nose. Secretions in the nose normally form an exceedingly thin, tenacious film of mucus on the surface of the cilia. Irritation by bacteria or other foreign material will cause increased secretion; only such abnormal states will cause the appearance of a transudate or exudate.

In the treatment of acute upper respiratory infections, e.g., chronic sinusitis, two basic problems are encountered—initiation of proper drainage and promotion of adequate aeration. Achieving these goals will provide both symptomatic relief and a more rapid return to normal function of the nasal mucosa.

In a nasal medication it would be beneficial to include an agent that would reduce the viscosity of the secretions. This would permit easier removal of secretions and crusts by the cilia and thereby permit better aeration. Of a group of agents tested, trypsin was found to be the only one effective for reducing the viscosity of sputum in vitro.[5] Thus trypsin should foster proper drainage and be an aid in overcoming one of the chief problems in the treatment of acute upper respiratory infections. In addition, it has been suggested that trypsin possesses anti-inflammatory properties.[6,7] This would be of aid in improving aeration by lessening inflammatory reaction and reducing swelling of the mucosa.

Trypp nose drops contain trypsin and phenylephrine, a nasal vasoconstrictor. Phenylephrine was selected for several reasons. It fulfills most satisfactorily the qualifications mentioned above for the ideal nasal sympathomimetic drug. (There is none that fulfills them perfectly). Phenylephrine has been in use for a sufficient period to be fully evaluated. It is effective and it is safe. In addition, the margin of safety is large (thirty ml. of phenylephrine ¼% contains approximately 80 mg., the usual oral dosage is 250 mg.).

The trypsin and phenylephrine have been put into a vehicle which results in an isotonic solution with a pH of 6.5. The effect of the final product on the cilia of rabbit trachea has been studied

by the method of Scudi, Kimura and Rheinhard[8,9] and found to be nontoxic and not interfering with normal ciliary action.

It was felt that this preparation, Trypp nose drops, containing trypsin presented a new and physiologic approach to nasal medication and clinical trials were undertaken.

### EFFECTS ON NORMAL NASAL MUCOUS MEMBRANES

Thirty children from 4 months to 10 years of age with no illnesses were treated for 10 days with the nose drops. Daily observations were made as to possible local irritation and sensitivity and as to the development of systemic toxicity or sensitivity. No such reactions were noted. (One child had epistaxis from "picking" on the second day of treatment; this was easily controlled and did not recur although therapy was continued for 8 days longer).

Fifteen of these children were retreated in a similar fashion after a rest period of one week to further ascertain development of possible sensitivity. There were no reactions noted.

To test the effects of nose drops with prolonged administration and large doses, 10 subjects were given the drops for 28 days with no toxic effects or local irritations. In 5 children given the drops in double the dosage, there was no sensitization or irritation reported.

### EFFECTS ON PATHOLOGIC NASAL MUCOUS MEMBRANE

202 infants and children with upper respiratory infections or acute exacerbations of chronic sinusitis were studied. The effects of the nose drops were evaluated on the basis of the following criteria:

1. Relief of symptoms and signs of acute inflammatory reaction, e.g., nasal congestion, edema, rhinorrhea.
2. Patient acceptance.
3. Irritation from or sensitivity to the medication, e.g., itching, burning or sneezing.
4. Possible toxic effects, e.g., drowsiness, irritability.

### DOSAGE

Infants below 1 year of age: 1 drop in each nostril 3 to 4 times a day.

1 to 5 years of age: 2 drops in each nostril 3 to 4 times a day.
6 to 12 years of age: 3 drops in each nostril 3 to 4 times a day.
Over 12 years: 3 to 4 drops in each nostril 4 times a day.
Ordinarily nose drops were given for no longer than 4 to 5 days.

Results were classified as excellent (immediate relief and complete therapeutic response within 3 days or less); good (gradual response as one would expect of any of the nasal vasoconstrictors) and poor (no response).

## RESULTS

Of the 202 infants and children studied, 175 (87%) had a response classified as "excellent".

Twenty-three of the children (11%) had "good" results and in 4 children (2%) the response was classified as "poor".

All except 3 of the children accepted the Trypp nose drops well and reported that there was no discomfort or unpleasant effect. Three children complained of a stinging sensation of several minutes duration following the use of the medication. On follow-up examination, there were no allergic reactions, e.g., sneezing, increased edema or discharge noted. No evidence of rebound phenomena was noted. No toxic effects were reported.

## COMMENT

As has been stated in the treatment of acute respiratory infections or exacerbations of chronic upper respiratory infections, e.g., chronic sinusitis, there are two basic physiologic problems, 1. Initiation of proper drainage, and 2. Promotion of adequate aeration. Achieving these goals will provide symptomatic relief and a more rapid return of normal function of the nasal mucosa.

The addition of chemotherapeutic agents and antibiotics to nose drops are of questionable value. In addition, there always exists the possibility of sensitization to these drugs and the development of resistant strains of bacteria. The use of a potent agent such as corticosteroids in a nasal medication for the symptomatic relief of upper respiratory infections would seem undesirable at this time.

This preparation (Trypp Nasal) contains trypsin and phenylephrine. Trypsin is a mucolytic agent which reduces the viscosity

of the nasal secretions. This helps the removal of secretions and crusts by the cilia and permits the vasoconstrictor, phenylephrine, to reach and act upon the nasal mucous membrane. Trypsin is also a non-steroid antiinflammatory enzyme which reduces edema. The trypsin does not interfere with the normal physiology of the nasal mucosa or with ciliary function. Phenylephrine has been found after many years of use to be an effective and safe nasal vasoconstrictor producing virtually no side reactions.

The clinical studies thus far would seem to suggest that a nasal medication containing trypsin in addition to a vasoconstrictor is more effective than the other nasal preparations now available.

## SUMMARY

1. A new nasal preparation which contains a buffered enzyme (trypsin) has been described. In the laboratory, this preparation is mucolytic, has some local antiinflammatory properties and does not impair ciliary function.

2. Clinical studies have indicated that there is practically no irritation or sensitivity with these nose drops.

3. In 202 children with upper respiratory infections or exacerbation of chronic sinusitis treated with Trypp nose drops, there was an excellent response in 175 (87%), good results in 23 (11%), and poor or no response in 4 (2%).

*Acknowledgment: We wish to thank the U.S. Vitamin and Pharmaceutical Corporation for supplying the Trypp® Nose Drops used in this study.*

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# *Pediatric Conference . . .*

THE ROOSEVELT HOSPITAL, New York
*June 17, 1959*

EDMUND N. JOYNER III, M.D., *Chief of Pediatrics, Presiding*
CHARLES H. BAUER, M.D., *Director, Premature Institute, The New York Hospital-Cornell Medical Center, Guest*

DR. JOYNER: Today our program is going to be on prematures, their care, and the advances in the care of prematures. As we have no cases to present, we'll get right down to the speaker who's been kind enough to come over. I'd like to introduce to all of you, Dr. Charles Bauer. You all know him, I think. He is Director of the Premature Institute, The New York Hospital-Cornell Medical Center.

DR. BAUER: Thank you very much, Dr. Joyner, for inviting me over here. It's a pleasure to come, especially since I do know just about everybody. I was asked to talk about advances in premature care, and I am embarrassed to say that I will not be able to fulfill my task because as we look through the literature to see what advances have taken place, we come to the ghastly conclusion that no earth-shaking advances *have* taken place . . . that we are still doing more or less what has been done for the last 10 or 15 years! What I will try to do is to refer to the work that was done by Levine and Gordon in 1942[1] when they published most of the data on which premature care is based today, and try to show you where some changes have taken place.

First of all, in terms of introduction, why do we even worry about prematures and premature care? Is it at all important for us as pediatricians, or for those who are in general practice, or for those who are in obstetrics?

The answer has to be "yes" because the incidence of prematurity is 7% of all live births, which is quite a staggering proportion. In

our own institution, The New York Hospital, it is somewhat less. They run approximately 4½ to 5%.

Not only is the incidence high, but the mortality also is tremendous. If we take the ten leading causes of death in the United States: the first is cancer; I think the second one is heart disease or vice versa, but anyhow the eighth leading cause of death is "prematurity." Just consider: approximately 250,000 prematures are born yearly, and yet this small number leads to the eighth cause of death! In terms of mortality, therefore, we have a staggering problem!

Have we found out anything about the causes of prematurity? No, we do not know what causes prematurity. We do know that certain factors, though, tend at least to precipitate or to accentuate the reason why prematures are born. For one thing, we have found out that there is a familial tendency. So often in our premature nursery, we find the same families, over and over again, having premature infants. We also find out that a large proportion of multiple births; twins, for example, account for approximately 15% of premature infants.

We find the maternal complications, for example, toxemia of pregnancy, antepartum hemorrhages, maternal illnesses, and trauma also play a large precipitating part, accounting for approximately 35% of all premature births. Many of these might be prevented by adequate pre-natal care.

However, if we take all the factors together, where we have some lead as to why an infant is born prematurely, we still come to the conclusion that in approximately 50% of premature births we can find no real reason why the mother went into premature labor. Therefore, in 50% of the cases, we really do not know why prematurity occurred at all.

Let's look at Table Number 1. [Table Number 1: Births and Perinatal Mortality at The New York Hospital] I would like you to see the tremendous increase of mortality in prematures compared to full-term infants. There are approximately 10 times as many deaths in prematures as there are in full-terms.

If we take over-all births and deaths, that is, both live and dead born, we find that again approximately 10 times as many prematures died as full-terms. The over-all premature mortality is approximately 20%.

TABLE I

BIRTHS AND PERINATAL MORTALITY AT THE NEW YORK HOSPITAL
(1932 through 1957)

| | *Live Births* | *Deaths* | *Deaths* | *Dead Born* | | *All Births* | *Deaths* | |
|---|---|---|---|---|---|---|---|---|
| | No. | No. | % * | No. | % ** | No. | No. | % |
| Total | 86,105 | 1,171 | 1.4 | 1,329 | 1.5 | 87,434 | 2,500 | 2.9 |
| Full Term | 82,066 | 571 | 0.7 | 852 | 1.0 | 82,918 | 1,423 | 1.7 |
| Premature | 4,039 | 600 | 14.8 | 477 | 10.6 | 4,516 | 1,077 | 23.8 |

# From 1951 through 1957, includes infants weighing from 1500 to 2499 grams
From 1951 through 1957, includes infants weighing from 500 to 2499 grams

* Rate per 100 live births
** Rate per 100 total births

We really have to analyze this in terms of birth weight. Doing this for the year 1957 in New York City, we find that infants with a birth weight of less than 1,000 grams, which is just a little bit over 2 pounds, have a mortality of 96%. That is a high figure. In our own Center, it is somewhat less, approximately 80%. If we can prolong gestation so that the birth weight increases to 1,000-1,500 grams, the mortality in New York City falls to one half, or approximately 50%; the exact figure is 48.6%.

If we can prolong it even further, to 1,500-2,000 grams, the mortality decreases even more: to only 16.7%. And if we can prolong gestation still longer so that we can get an infant somewhere between 2,000 and 2,500 grams, the mortality falls to approximately 4.4%. Therefore, the first aim we have in premature care is to prolong the gestation period of the mother; that is, prolong the time before the infant is born. But let us not forget and become indifferent about the larger prematures, those of 2,000 grams to 2,500 grams. Remember we still have approximately a 4% mortality, which is still staggering and approximately 10 times as high as full-terms; therefore we should not be too complacent just because an infant weighs 2,000 to 2,500 grams.

Levine and Gordon in 1942[1] discussed the physiologic handicaps of the premature infant. I would like to show you what was known at that time and where, if at all, we have made any changes—any improvements.

The first handicap of prematurity, respiratory distress, is the leading cause of death in premature infants. In terms of anatomical

studies that have been performed on premature infants, we know that at first alveoli are lined with columnar epithelium, which later decreases in size to transitional epithelium, which finally becomes squamous or respiratory type epithelium. The high epithelium is thus an anatomic factor contributing to respiratory distress in the immature infant. But other systems in the body also play their part. First of all, the nervous system. We know that many of our infants have a certain nervous system immaturity. They cannot respond to various stimuli as well as the full-term infant. They have a weak gag and cough reflex, and as a result they choke or aspirate quite easily.

As far as the vascular system goes, we know that the vascularity of the pulmonary capillaries is greatly reduced, so that the oxygen-carbon dioxide exchange is decreased.

The sparseness of the elastic tissue results very frequently in atelectasis; also, hyaline membrane formation takes place. I shall discuss the latter factor, hyaline membrane formation, in somewhat greater detail shortly.

We all know that there is a very weak muscular system; we know that the respiration, as we watch the small, premature infant, is not normal thoracic as we see in full-term and adults, but is an abdominal type. In fact, small infants need every muscle in their bodies to enable them to breathe. The belly is used; the abdominal muscles are used; the diaphragm is used; and so is the chest. In addition, they have a rather soft and pliable chest cage, or thoracic cage; so pliable that even when we want the cage not to move, you can see the sternum contract with every cycle of inspiration-expiration. You can see the sternum move in and out as if it were made of plain cartilage, which it partially is. And finally, there is some persistence of fetal hemoglobin, which may or may not be a factor in the respiratory distress in these infants.

Since 1942, physiologists—some of them working at Columbia, some in California, some in Europe—have conducted systematic studies on whether these infants do or do not actually have any chemical changes associated with their respiratory distress. Every study, in addition to the ones mentioned, shows that a premature infant, when he is born, has a greatly decreased oxygen saturation at time of birth, that his $PCO_2$ is greatly increased, that is, he already has too much carbon dioxide, and thus the serum pH of a premature infant is much lower than in a full-term infant or adult.

To illustrate this, the pH of a normal adult is approximately 7.45. In a premature infant with no respiratory distress, it is as low as 7.26: extreme acidosis.

In depressed infants, the pH goes down to as low as 7.04, which in an adult is practically incompatible with life; and in an extremely depressed premature infant the pH falls below 7, as low as 6.7, which in an adult is incompatible with life; therefore acidosis, respiratory acidosis, is probably one main factor why many of these children do get into trouble. One of the modern concepts in treating these children is to try and correct this acidosis and to correct it quickly.

What have we learned as far as treating infants with respiratory distress, which, as I mentioned before, is the leading cause of death in the prematures?

The first and most important thing to do has been done for many years. I again want to emphasize that one must establish an airway. You have to establish an airway before an infant can breathe. The simplest way of establishing an airway is just to keep the head a little bit lower than the trunk, to use a bulb or a rubber catheter to suction the mucous out of the mouth and nostrils.

It is very rarely that you need anything else besides this. However, there are a number of infants who do require more intensive resuscitation. In some infants a little bit of oxygen just blown over their face helps a great deal in stimulating them, and this is a common practice in most delivery rooms. We want to warn you about using oxygen. If you have a blue infant who needs oxygen, you must use it. An infant who is cyanotic, an infant whose heart rate is around 100 or less, an infant who is only taking gagging types of respiration or no respiration at all needs more intensive resuscitation. In recent years we have found mouth-to-mouth respiration the most effective type. This is something that was unheard of five or ten years ago, but we now believe this is the safest and most effective. By this I do not mean that an untrained person just goes and blows air into an immature infant. You would be surprised how much pressure you would use, you might rupture the alveoli. But somebody who has practice in mouth-to-mouth resuscitation can soon acquire the skill of giving approximately 25 to 35 or 40 centimeters of pressure by just blowing air into an infant. We have found in our own institution that very few doctors are using this method of resuscitation, because they don't have enough

time to practice or make use of this. We therefore use a mechanical aid to produce positive pressure.

Work done by Wilson and Farber[2] shows that at least 25 centimeters of water pressure on the trachea is necessary to expand the lung in full-term infants. More recent work indicates that pressure as high as 60 centimeters is needed. However, pressure over 40 centimeters can lead to alveolar rupture. To prevent this, Day[3] advocates the use of high pressure for fractions of a second. Goddard[4,5] has summarized this by stating (a) that beginning patchy aeration of the unexpanded lung of the human newborn was achieved with a positive pressure of 30 centimeters of water, (b) that uniform expansion was achieved at pressures of 50 to 60 centimeters in the closed chest, and (c) 0.2 to 0.3 of a second is a safe time interval to apply such pressure.

Thus, initial resuscitation should start with the application of a positive pressure of 50 to 60 centimeters of water. This can be applied safely over a 0.2 to 0.3 second interval when given by the Goddard-Bennett-Lovelace Infant Hand Resuscitator[6]. Twelve to twenty-four impulses are given in the first minute, which is followed by suctioning. This usually enables the infant to take a breath. Once voluntary respiration is achieved, the pressure should then be reduced to 40 centimeters for another twelve to twenty-four impulses, followed by further suctioning, and finally the pressure can be decreased to 20 to 30 centimeters of water after the infant has established good respirations.

We like the Infant Resuscitator inasmuch as we also use it frequently in our Premature Nursery on infants who develop respiratory distress. Once the infant has breathed on his own, pressures of 30 to 40 centimeters usually suffice; these pressures can then be reduced to 20 to 30 centimeters, and finally to as low as 5 to 10 centimeters.

Late experimental work recently reported at a meeting in Buck Hill Falls suggests that respiratory distress may be secondary to cardiac abnormalities. No one knows whether cardiac enlargement is the cause or the result of the respiratory distress. However, there is preliminary evidence of some peripheral edema, cardiomegaly, and even cardiovascular insufficiency associated with the syndrome of respiratory distress. Much research in the next few years is needed in this field as well as in investigation of the severe acidosis seen in the respiratory distress syndrome.

Hyaline membrane disease is a very frequent cause of abnormal pulmonary ventilation. Pathologically, it is nothing but an eosinophilic staining membrane that lines alveoli; very frequently it is associated with atelectasis. Hyaline membrane disease occurs frequently in a premature infant; also in infants of diabetic mothers; and in infants born by Caesarean Section. It is a pathologic diagnosis; however, we now have enough clinico-pathologic evidence to enable us to make a fairly safe clinical diagnosis. We usually find such an infant in good condition at the time of birth who develops increasingly rapid respirations which progress to grunting, dyspnea, retractions, and cyanosis. There is some evidence that these infants actually are in distress at birth.

Recently, we have followed these children by x-rays. These show a diffuse fine hazy granular pattern throughout the lung fields.

Hyaline membrane disease is no longer uniformly fatal. The treatment for the hyaline membrane syndrome is purely symptomatic. As these children have respiratory distress, they usually require oxygen-mist environment. As atelectasis usually is associated with this, intermittent positive pressure is indicated. We also advocate the use of anti-microbial agents to treat any coexisting infection or aspiration. The simultaneous use of various electrolyte solutions is also now under investigation. By using such a regimen we have found that many of the children do recover and never reach the pathologist.

A second handicap of a premature infant, which I should like to discuss in some detail, is his erratic control of body temperature. We all know that the body temperature is usually 34 or 35 degrees C at birth. Everybody gets very upset about this, and the infant is warmed to what is considered a normal 37 degrees, or somewhere around this.

Now, why do these infants have faulty control of body temperature? There are three main reasons: (1) Low total heat production, due to body inactivity and feeble muscular development[1]; (2) Excessive heat loss, both by radiation as well as by convection, when the infant is exposed to a cold environment. The reason for this is that the premature infant has a body weight very disproportionate to its large surface area, as well as little fat and insulating subcutaneous tissue; (3) Rapid over-heating. We only have to accidentally overheat an incubator and we can fry such a pre-

mature baby. The premature infant cannot cope with excessive heat due to underdevelopment of sweat glands. These factors have been known for a long time.

Let us see what recent advances have been made in this field. To do this, we have to review briefly the work accomplished by Dr. Silverman and his associates at Columbia University.[7,8] The first thing studied was the addition of detergents, as for example, Alevaire to an infant kept in an environment of 89 degrees F compared to 80-90% humidity without Alevaire. They reported that there is no difference in mortality whether or not nebulized water mist, Alevaire, or 80-90% humidity is used as long as environmental temperature is maintained at 89 degrees. Therefore we at this time do not use detergents in our premature nursery.

The effect of environmental temperature on survival was studied next. All previous studies had been conducted with an environmental temperature of 89 degrees F. Dr. Silverman now changed the temperature of incubators to 84 degrees, keeping one group at 80-90% humidity and the second group at 55% relative humidity. The 55% relative humidity was selected because the original work in Boston of Dr. Blackfan in 1933 had demonstrated that infants kept in 55% relative humidity had a better survival rate than infants kept at 30%. To no one's surprise, it was demonstrated that infants maintained at 80-90% relative humidity had a higher survival rate than those infants that were maintained at 55%. Now, the question arose: was this due to the fact that there was an increased humidity, or was there another factor involved?

In analyzing his studies, Dr. Silverman found infants maintained at 80-90% relative humidity had a body temperature of ½ to 1 degree F higher than those infants kept at a relative humidity of 55%. Therefore the next question that came up was whether possibly the environmental temperature had something to do with the higher survival rate. Therefore Dr. Silverman next kept the relative humidity at 80-90% but varied the environmental temperature in two groups of infants. One group of infants was kept at 89 degrees F environmental temperature; the second group of infants was kept at 84 degrees F environmental temperature, and now to the surprise of most people it was found that infants kept at 89 degrees F environmental temperature had a *higher survival rate* than infants kept at environmental temperatures of 84 degrees F.

Therefore, it may not be the humidity but actually the environmental temperature itself that has something to do with increasing the survival rate.

One last question which has not yet been answered: Is it possible that the body temperature itself may have something to do with increasing the survival rate? At this time Dr. Silverman is studying the problem. Knowing that the higher environmental temperature of an infant increases his chances of survival, he now keeps the body temperature at a constant level of 98.6 degrees F by thermostatic control so that this variable is removed. One group of infants is being maintained at 80-90% humidity while another group is being kept at 55% relative humidity. If humidity makes a difference, then there should be a higher survival rate in those infants maintained at higher humidity. If, however, it is found that there is no difference in mortality, we will have to conclude that all increased humidity does is keep infants' body temperature at a higher level, and it is really the higher body temperature, and thus the higher environmental temperature, that may be the main reason for improved survival. These studies are now in progress, and we are eagerly awaiting a report on them.

I should like to mention that in Europe, especially in some of the Scandanavian countries, the exact opposite of course is used, and, there, people believe in keeping body temperature low; that is, keeping infants at hypothermia, may increase the survival rate by decreasing metabolic requirements and thus the oxygen demands.

These two conflicting views will be resolved only by further laboratory study. Our view at the present time is that we should raise the infant's temperature to a level of approximately 98 to 98.6 degrees F, and keep humidity somewhere between 80-90% on all premature infants with any respiratory distress. This is achieved by keeping the isolette at "Full Humidity."

Another special problem in premature care is the relative immaturity of the kidneys. Pathologically, it has been shown that infants weighing less than 1,000 grams have virtually no fully developed nephrons. Therefore, from a renal point of view, this is practically incompatible with life.

We also have histologic data to confirm the relative renal immaturity. In the full-term infant, there is a well-formed nephron with a very thin basement membrane and ample vascularity. In the premature, however, there is cuboidal and even columnar epithe-

lium in the nephron. Therefore, purely from a mechanical point of view, these nephrons are quite underdeveloped compared to those of a full-term infant.

Studies done by Dr. Barnett have shown that the premature infant is at a great disadvantage. The glomerular filtration rate, renal plasma flow, as well as tubular excretion in a premature infant is much less than that in a larger infant or in an adult.

All these factors have been known for many, many years.

Studies during the last few years have shown that in terms of renal function, a premature infant can dilute the urine just as well as an adult. However, they are unable to excrete as concentrated urine as an adult. Now, what does this mean? It means, very simply, that if we give fluids to an infant, especially a premature infant, we must use very dilute, hypotonic solutions. Let me illustrate this with an example.

If we withhold fluids from a premature infant, he can concentrate his urine to a maximum of 700 mosm/L or 1.4 ml of water are needed to excrete 1 mosm of any solute. Compare this to an adult who can contrate urine to 1400 mosm/L and thus needs only 0.7 ml of water to excrete 1 mosm of any solute. In other words, a premature needs twice as much water as does an adult to eliminate the same quantity of solute. Let us now give 0.9% saline to these two individuals. Saline contains 300 mosm/L or 30 mosm of solute per 100 ml. To eliminate these solutes, an adult will require 30 x 0.7=21 ml of water. Thus, for every 100 ml given, he can use 100–21=79 ml. of water. A premature however, in the best possible condition will require 1.4 ml of water for excretion of every mosm of solute; this is 30 x 1.4=42 ml. Therefore, out of 100 ml given, the infant at best can save 100–42=58 ml. of water. A sick or very feeble premature, however, may be able only to concentrate to one half as well: Let us say 350 mosm/L; using these same calculations it becomes obvious that the infant might not be able to save and thus utilize any water at all if normal saline is given.

In our own institution we have found that if we have to give supplemental fluids, we like to use a hypotonic 1/3 physiologic saline solution. We find that this is one which the premature infant tolerates well. I am always appalled when visiting other nurseries to find written orders that the premature infant should be clysed

with equal amounts of 5-10% glucose and water and "normal saline."

The premature infant cannot excrete these electrolytes. You overload his renal capacity. You therefore must use a hypotonic or dilute solution if you use supplemental fluid therapy on an infant.

We have learned a great deal about diminished alimentary tolerance in the premature infant. It is this handicap that perhaps has caused most arguments within the last few years: is there or is there not a specific optimal diet for the premature infant?

Very delicate balance studies done by Dr. Levine and Dr. Gordon, during the late 1930's and early 1940's,[1] have shown that there is a definite diminished alimentary tolerance for certain substances. Their studies have shown that a premature infant, for example, is not able to handle fat as well as a full-term or as an adult. This is perhaps best illustrated by presenting data on a set of twins where the amount of fat in the diet was varied. When the fat in the diet was raised from 1.8 grams to 4.7 grams per kilogram body weight, the percentage of fat in the stool was increased. Also, the weight gain dropped to only half of that as to when the fat was lower.

We know that the optimal weight gain of the premature infant is approximately 13 to 14 grams per kilogram per day. By increasing the dietary fat, this optimal weight gain is cut in half. More recent studies have shown that unsaturated fatty acid fats in the form of vegetable oils are much better absorbed than saturated fatty acids in the form of animal fats. Let it suffice to say again that there is very little dispute about the fact that premature infants are not able to handle fat as well as full-term infants or adults, but the use of unsaturated fatty acids may modify this concept.

Carbohydrates in general are fairly well tolerated by most premature infants. At least for the moment no argument is raised about this.

But now, how about proteins? Protein is a story all by itself, and we could spend hours just talking about the protein requirements of a premature infant. Let it suffice for the moment that Levine and Gordon's work shows that an infant, to gain optimum weight, requires a high-protein diet of approximately 5-6 grams per kilogram per day.

Let me mention that within the last few years more and more authors have disagreed with Levine and Gordon. Kagan and

others have argued that it might not be the high protein in the premature infant's diet that is responsible for the adequate weight gain, but that it may be the high ash content present in cow's milk protein that is responsible for the high weight gain. They believe that the weight gain therefore is due to accumulation of edema fluid. Another distinguished group of investigators believe that a diet as low as 2 or 2½ gm/kg of protein per day may be adequate.

The two camps are just about equally divided at this time, so that neither the World Health Organization nor the American Academy of Pediatrics has recommended the optimal protein requirements in a premature infant.

A symposium sponsored by the American Food Council is scheduled for this year, at which time the issues of both sides, "High-protein vs. low-protein" will be aired. However, this argument will not be resolved until some detailed controlled studies will have been completed. Dr. Levine and his group of investigators now are conducting blind studies where infants are fed low-protein, in-between-protein, and high-protein diets in which the ash content also is varied. It will take approximately two to three years to have an answer as to whether low-protein diets are just as good as high-protein diets. If we can show that low-protein or in-between-protein is as optimal as a high-protein diet, it will be of tremendous value, especially for the more backward countries of Asia, Africa, and South America, where high-protein diets are practically impossible to obtain because of the expense. Also, it must be remembered that the cheapest form of feeding is human milk, and this is a low-protein diet, containing approximately 2 grams instead of 5-6 grams of protein as recommended earlier. Until this argument is settled, let me show you what, at the present time, is our concept of an optimal diet for the premature infant: A premature infant should have daily approximately 150 cc per kilogram of fluid; the caloric content of the diet should approximate 120 calories per kilogram. We at present believe that a premature infant should have a high-protein diet for optimal weight gain and survival. This will require 5 grams per kilogram of protein, 18 grams per kilogram of carbohydrate, and 2 grams per kilogram of fat. The calcium content is approximately 150 milligrams per kilogram; phosphorus is 130 milligrams per kilogram.

To get this diet we use a one-half strength skimmed milk formula, available as "Alacta" or "Dryco".

In addition to the fluids, protein, carbohydrate, and fat content, we believe premature infants require supplemental vitamins, including vitamin A of approximately 3,000 International Units per day, vitamin D of 1,000 International Units per day, and vitamin C of approximately 50 milligrams per day.

We have no evidence that a premature infant requires any vitamin B complex; however, vitamin B complex is not harmful and is used by many physicians. We do not believe that vitamin E is needed at the present time, although Dr. Gordon has some evidence that it may decrease red blood cell fragility. Vitamin K, which once was routine, is given now as Vitamin $K_1$-oxide in a dose of approximately 1 to 2 milligrams. We do not believe vitamin K should be given or repeated routinely, as higher doses have led to kernicterus.

The most important work on anemia of prematurity is that of Dr. Smith and Dr. Schulman, published in 1954,[9] in which it was shown clearly that the anemia of prematurity was due primarily to hypoactivity of the bone marrow; this is the reason why the hemoglobin drops so sharply during the first four to six weeks. There is nothing that one can do during this time to stimulate the bone marrow; no iron or other medications help. It formerly was the practice to give transfusions to all small premature infants; we know now, however, that this only depresses bone marrow activity even further at a time when normal regeneration of hemoglobin is at hand[10]. We therefore do not give transfusions to premature infants on the basis of anemia alone, even if the hemoglobin decreases to as low as 6 gm/100 ml. In cases of hemorrhage, hemolytic disease, or infection, transfusions may have to be employed.

The second phase of anemia in these infants is the development of iron deficiency; this iron deficiency does not take place, however, until the infant is approximately 2 to 4½ months of age. The reason for this is that the premature utilizes the iron made available by the destruction of his own blood, but by 2½ months of age this is used up and iron is necessary for the synthesis of additional hemoglobin and for iron storage. It is our practice therefore to start iron with all premature infants at approximately 2 to 2½ months of age, but *not* before that time unless there are additional complications. Within the last year or two, safe intramuscular preparations of iron have become available. We would advocate their use only in premature infants where follow-up would be poor,

and also in the low economic group where you could not be sure that the mother would give iron to the premature after leaving the hospital. We do feel that, otherwise, the oral method is a safer one of giving iron.

Increased capillary fragility has been seen by all of us. The greater bleeding tendency of premature infants we now know is due to a reduction of all factors in the clotting mechanism and not just to hypoprothrombinemia, as was once believed.

The increased content of body water present in prematures was once thought to be of great advantage; we know now that the increased content of body water may actually be a handicap, as it may be one of the reasons why a premature infant is so much more susceptible to infection.

Hepatic immaturity is a factor that is becoming more and more of a problem. We know that premature infants have a greater tendency to be jaundiced than do full-term infants. Should we do anything at all about this?

Among the work that is being done at the present time there are enzyme studies, and we know that one of the enzymes that is low or lacking in these infants is an enzyme known as "glucuronyl-transferase". This is the enzyme which converts indirect bilirubin to the direct form of bilirubin. The big question still remains: should one do anything to remove the indirect bilirubin before hepatic maturity, or, as we now know, before enzymes develop in sufficient quantity to convert the indirect form of bilirubin to the direct form of bilirubin? There is no clear-cut answer. Some investigators feel that whenever the indirect bilirubin rises close to 20 mg per 100 cc, you should do an exchange transfusion. We are somewhat more conservative in our own institution. We feel that there is a clear indication for exchange transfusion if there is a hemolytic process complicating the hepatic immaturity. We do feel, however, that if you have just hepatic immaturity or lack of enzymes like glucuronyl-transferase, an attitude of watchful waiting may be advisable because we know that there is still a high mortality with exchange transfusions, especially in the small premature infants. Also there is some evidence that hyperbilirubinemia in prematures may not lead to kernicteras. We therefore have to individualize and not rush into exchange transfusions just because a premature infant does have a tendency to get jaundiced. Only studies in the next few years will elucidate whether all pre-

matures should receive exchange transfusions if and when the indirect bilirubin rises close to 18 or 20 on the fifth or sixth day due to hepatic immaturity.

Another handicap of the premature infant is a tendency to develop retro-lental fibroplasis. We have practically eliminated this iatrogenic problem. There still are sporadic cases of retrolental fibroplasia but a cooperative study[11] has shown without doubt that oxygen is the incriminating factor and that premature infants should not be given oxygen routinely as was once the practice.

The premature infant should be given oxygen only when specifically indicated. The specific indication is cyanosis and other signs of respiratory distress. If oxygen is needed, it should be given for as short a period of time as possible and should not be given just because a nurse in a premature nursery feels that the infant just "doesn't look right". One must get the infant out of the oxygen just as soon as possible. If you have to use oxygen, use it under 40% if at all possible, and I say if at all possible because I am sure there are times when you may need greater amounts of oxygen for survival. As a general rule, however, do not use oxygen at all if you can do without it; if you have to use it, use it for short periods of time and keep it under 40%.

Since publication of the paper of Dr. Levine and Dr. Gordon, we have felt the need of adding to their list two other handicaps of prematurity. One of these factors is infection. Infection in a premature infant has become more and more of a problem—as is the case with all newborn infants. The trend since the 40's has changed. It is no longer the gram-negative organism which is responsible for epidemics; it has become, now, the gram positive organism, namely, the staphylococcus. To be sure, the mortality in systemic gram-negative infections still is very high.

Work in the last few years by Dr. Eichenwald and others has shown that the biggest hazard in the staphylococcus problem is not the nurse, is not the mother, but is the infant itself. If an infant develops a staphylococcus infection, he is the source which spreads it from one infant to another. Now, naturally, for the original infant to get the staphylococcus infection, he has to be in contact with a carrier. We therefore urge that any personnel working in any nursery be screened very carefully, that cultures be taken frequently, and that if a nurse or parent has signs of staphylococcus infec-

tion he or she be barred from the newborn until this has cleared up. We now culture all of our infants prior to discharge.

There is no good and simple staphylococcus treatment at the present time. Once an infant becomes a carrier of any 80-81 staphylococcus, it can not be completely eradicated; all you can do is follow such infants closely for any signs of overt infection.

In some parts of the country this problem has become so severe that new hospitals have been built and whole nurseries have been remodeled. In our own unit, an entire nursery has been reconstructed because of this problem. We use what is known as the "unit plan," whereby infants enter the nursery unit at the same time and are discharged at the same time, so that all infants are cleared out before new ones are brought in. We keep no more than four infants in one of these units and allot at least 30 square feet of space for each baby; thus, should one of those infants develop an infection it would not contaminate the whole nursery but at worst only the three other infants in the unit with it.

As far as antimicrobial therapy is concerned, we don't know what the answer is. We have stopped using routine prophylactic antibiotics just because an infant is premature. We do treat, however, those premature infants in whom there are specific indications, such as premature rupture of the membranes, infection, or recent history of infection in the mother. I cannot tell you what correct antimicrobial agent to use. In many centers, penicillin or chloramphenicol were used until very recently. It now has been shown that the latter drug is toxic to the premature infant. It caused abdominal distention, a shock-like state, and even death. The reason for this was the excessively high dosage. The average dose was up to 100 milligrams per kilogram, and when blood levels were taken in these infants, they showed toxic levels. Perhaps if lower doses such as 30 milligrams per kilogram are used, this drug may again be a good agent.

Gantrisin is contra-indicated because it has been associated with kernicterus.

In our own unit, research by Dr. Baum and Dr. Eichenwald and others has shown, for example, that penicillin V is well absorbed orally if given in high enough doses. The dose recommended is approximately 20,000 units per kilogram per day, given every eight hours. We hope eventually to be able to replace all intra-

muscular antibiotics with oral preparations such as penicillin V to combat the growth of both gram-positive and gram-negative organisms. Suffice it to say, there is no one 100% effective anti microbial agent at the present time. I urge you again to avoid the sulfas and high doses of chloramphenicol, which have increased rather than decreased mortality. Use antimicrobial agents only for specific indications!

Finally, I would like to mention the special handicap of a premature infant who is also the offspring of a diabetic mother. Very little progress has been made in this field. The over-all mortality of these infants is approximately 15-20% regardless of the therapy used.

Three years ago at Carmel, California, Dr. Reardon reported that she, by using an entirely different regimen in these infants, has greatly reduced mortality. She feels that all the infant offspring of diabetic mothers have a relative hypoglycemia, a relative hyponatremia, hypoproteinemia, lowered pH and increased $pCO_2$. She feels therefore that optimal therapy should include the use of antibiotics, humidity, and careful observation plus early fluid therapy. She feeds these infants within the first two hours of life and uses a solution that contains equal amounts of 5% dextrose and water and .45% saline. This is obtained by mixing equal amounts of 10% dextrose and water with .9% physiologic saline. She feels that this solution will correct the hyponatremia and possibly the hypoglycemia and will help to correct the pH. In severe cases of acidosis, sodium bi-carbonate ($Na\ HCO_3$) is also added. The solution at rate of 60 cc/kg/24 hrs is given for 18-24 hours.

All that we can say is that her figures (which have not yet been published) give a mortality of four out of 60 treated cases compared to six out of 15 deaths in untreated cases. If controlled studies can show that infant mortality is really reduced, and these studies now are going on in various centers, this new approach with various modifications will be useful not only for offspring of diabetic mothers but possibly for all infants who show respiratory distress. Severe acidosis is the common denominator in these conditions, and solutions using glucose, insulin, as well as sodium-bicarbonate are now under investigation. Remember, all infants of diabetic mothers are immature infants even if they weigh 4,000 grams; they also have the added handicap of being in severe electrolyte imbalance and acidotic. We try to keep the immaturity problem at a minimum by

waiting until approximately 37 weeks of gestation before delivering these infants.

To summarize, what I have tried to do is to point out some of the handicaps of prematurity and what progress has been made in the past ten to twelve years; finally, I tried to stress the main areas where additional research is needed. These include:

1. The cause and therapy of respiratory distress and acidosis.
2. The optimal environmental temperature and humidity for these infants.
3. The infant's optimal diet—should it be a high-protein or should it be a low-protein diet?
4. A better method of preventing and combating infection in these infants, including the proper choice of antimicrobial agents.
5. Finally, the management of infants of diabetic mothers.

DR. JOYNER: Thank you very much.

I know, although the time is late, that Dr. Bauer will be kind enough to answer some questions if anybody has them, and I'd like to start by asking him a couple of them.

One thing that's always disturbed me, both in prematures and in full-term babies is the didactic ruling of when you start feeding a baby. I can't see any reason sometimes with a perfectly good premature to keep him from getting fluids and water, especially from what you told us about this, for 24 to 48 hours, if he doen't have very much mucus and doesn't have any trouble.

The other think that I was hoping you would say something about was the use of tube feeding; what the indications and what the dangers are?

DR. BAUER: First of all, as to when should a premature be fed, I feel as Dr. Joyner does, that there should be no strict rule. I think you have to individualize every premature infant.

In general, the worse condition the infant is in, the more respiratory distress it shows, the longer we used to stay away from oral feedings. I feel there is no reason at all, if an infant is in good condition, to delay feedings for more than the first 12 hours. Our initial feeding is a 5% glucose solution.

Now, if the studies of Dr. Reardon are substantiated, our whole concept about feeding will change.

We might find that the more severe respiratory distress an infant has, the sooner we should start feeding him in an effort to correct the pH; Dr. Reardon feels that if an infant has respiratory distress you should try and feed him parenterally at first. If the infant is in good condition she feeds by mouth within 4-6 hours.

I would like to mention briefly tube vs. gavage feeding. First of all, I think every infant should be fed by nipple if he can suck. In general, and this is just a generalization, most infants around 1500 grams are able to have nipple feedings, and you should try them on nipple feeding before using any other method. If you find out an infant cannot suck well, then you have to use one of the more artificial forms of feeding.

We did some studies a couple of years ago at The New York Hospital to see if there was any difference between indwelling tube and gavage feeding, and came to the conclusion that if you have trained personnel who know how to gavage-feed, it does cause less mucus and less irritation in an infant than if you have a constant indwelling polyvinyl feeding-tube. If, however, you do not have skilled personnel available on every shift, it is far less hazardous to use an indwelling polyvinyl tube. There have been very few complications. We have never seen esophagitis or any ulceration clinically or at post mortem. The only thing we have seen is an increased amount of mucus when we use the indwelling tube.

Therefore our recommendations would be follows.

1. Nipple-feed as early as possible.
2. If you have to use an artificial method, if you have trained personnel available for every shift, use gavage and avoid an indwelling foreign body. If you do not have experienced personnel available for every shift, use an indwelling polyvinyl tube; it is safe and works out perfectly well in most cases.

DR. JOYNER: How long do you leave it there? Do you change it?

DR. BAUER: We, in our unit, change it every 5-7 days. I must admit though at times I have forgotten to change the tube, and I could see no harm keeping the tube in place three more days. We try not to forget to change the tube, but I don't think you have to be religious about it. In some places, they change every 3-5 days.

DR. JOYNER: Any other questions?

QUERY: Is there any fixed rule about when you start vitamins?

DR. BAUER: No; in our unit we start vitamins at the age of 7 days.

DR. JOYNER: Any other questions?

QUERY: In view of poor renal function, what dosage of antimicrobial agents is given.

DR. BAUER: It varies in practice. Let us go back again to the use of chloramphenicol, for example, where there is a tremendous accumulation of this drug in the blood, so that when a single dose of 100 mgm/kg is used, toxic levels may remain for three days. We therefore would use only 15-25 mgm/kg. We have found out that drugs like tetracycline are poorly absorbed even more poorly excreted, and thus again will accumulate. Intramuscular preparations give completely erratic blood levels at present therefore should not be used. We have shown that Bacitracin in overwhelming staphylococcus infections, given in a dose of 800 U/kg/per day is relatively safe. Kanomycin also may be safe if given in a dose of 15 mgm./kg./day.

There are other drugs, like the sulfa drugs, that have been found to be toxic, and I'm sure as more drugs are analyzed, we'll find many other ones which will have toxic effects too. None of us knew about chloramphenicol until the last year or so, and I'm sure many other so-called routine, safe drugs will be found to have more serious effects in prematures. Use as few drugs as you can. Who would have believed a few years ago, that sulfa drugs, as well as salicylates and Caffein Sodium Benzoate, all may increase hyperbilirubinemia!

QUERY: Dr. Bauer, at what stage is renal function established in a fetus?

DR. BAUER: I'm sorry I can't tell you this. All I know is that the studies by Potter have shown that a 100% underdeveloped nephrogenic zone exists in infants of 20-29 weeks of gestation. We know there are infants weighing about 800 grams (I think our lowest was about 600 grams) who do survive; so we know there is some kidney function present.

I don't think there is a rule. All we can say is renal immaturity persists right up to the full term infant; anatomically we find immature glomeruli up to 2,000 gram infants; above 2,500 grams

all glomeruli are usually mature except in offspring of diabetic mothers where immature glomeruli are present even at 3,000 grams. The more immature the kidney is—by this we mean the less the birth weight and the gestational age is—the more careful you should be about overloading the body with too much fluid or using too concentrated a fluid. I do not know exactly at what stage renal function is established but again urge that one use only hypotonic solutions.

QUERY: Isn't there much to be learned still of the cardio-pulmonary physiology at the time of birth?

DR. BAUER: There are studies going on in Boston, Baltimore, California, Scandinavia, and probably many other areas as well. At present the role of the physiologically open ductus is under investigation. Hyperkalemia has already been mentioned. Blood pressure studies also are in progress.

QUERY: How about the problem of maternal anaesthesia?

DR. BAUER: We find that the more sedation is used, the more lethargic an infant is born and the higher is the incidence of respiratory distress. The less sedation you can give a mother, the more vigorous a premature infant is born.

DR JOYNER: Any further questions?

If not, we'll thank Dr. Bauer again for this very interesting and stimulating talk.

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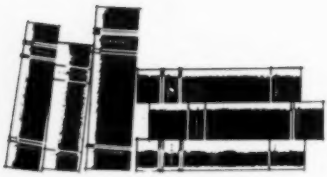

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MICHAEL A. BRESCIA, M.D.

DIABETIC MANUAL. Edited by Elliott P. Joslin, M.D., Sc.D., Tenth Edition. Pages 290, cloth. Lea & Febiger, Philadelphia, 1959. Price $3.75.

The well-known Dr. Joslin has issued a tenth revision of his classic primer for diabetic patients and those concerned with their care. For the diabetic or for the diabetic's mother and or family, this book should be a must. The book is written in simple language, readily understandable and divided into thirty-two (32) short chapters. All aspects of diabetes mellitus that a patient might be interested in are discussed with considerable clarity and with a pleasant individuality of style. History of diabetes, diet, insulin and orally acting hypoglycemic drugs, coma, insulin reactions, prognosis and when to visit the doctor are the many topics discussed.

Dr. Joslin's views on the need for strict dietary control are well known. Despite the rise in recent years of an opposition group that permits much more latitude, it still remains desirable for diabetic patients to receive indoctrination such as this book conveys to the diabetic.

Most impressive of Dr. Joslin's style and clinical philosophy is his statement: "I look upon the diabetic as a charioteer and his chariot is drawn by three steeds named 1. Diet, 2. Insulin, 3. Exercise. It takes skill to drive one horse, intelligence to manage a team of two, but a man must be a very good teamster who can get all three to pull together and to succeed he needs instruction and practice." All physicians should recommend this book to their diabetic patients or family where children are involved. It would certainly help in controlling your diabetics in practice far more than verbal advice can ever accomplish. JOSEPH M. COVELLI, M.D.

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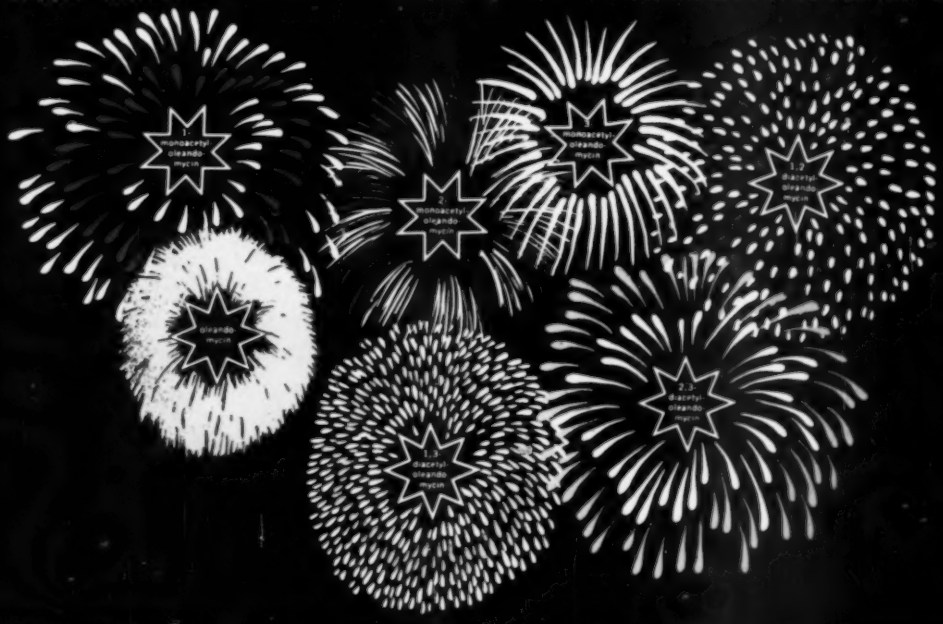


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1. English, A. R., and McBride, T. J.: Proc. Soc. Exper. Biol. & Med. 100:880 (Apr.) 1959. 2. Celmer, W. D.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 277. 3. English, A. R., and Fink, F. C.: Antibiotics & Chemother. 8:420 (Aug.) 1958.

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*Livingston, S., and Petersen, D.: New England J. Med. 254:327 (Feb. 16) 1956.

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